

UNITED STATES  
SECURITIES AND EXCHANGE COMMISSION  
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT  
PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

Date of Report (Date of earliest event reported): January 3, 2018

**VistaGen Therapeutics, Inc.**

(Exact name of registrant as specified in its charter)

**NEVADA**  
(State or other jurisdiction of incorporation)

**001-37761**  
(Commission File Number)

**20-5093315**  
(IRS Employer Identification Number)

**343 Allerton Ave.**  
**South San Francisco, California 94090**  
(Address of principal executive offices)

**(650) 577-3600**  
(Registrant's telephone number, including area code)

**Not Applicable**  
(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instruction A.2. below):

- Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
- Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
- Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
- Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (17 CFR 230.405) or Rule 12b-2 of the Securities Exchange Act of 1934 (17 CFR 240.12b-2)

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act

**Item 7.01 Regulation FD Disclosure**

See Item 8.01 below.

**Item 8.01 Other Events.**

On January 3, 2018, VistaGen Therapeutics, Inc. (the “*Company*”) issued a press release announcing that the U.S. Food and Drug Administration has granted Fast Track Designation to AV-101, the Company’s lead central nervous system product candidate for development as a potential adjunctive treatment for Major Depressive Disorder. A copy of the press release is attached to this Current Report on Form 8-K as Exhibit 99.1, and is incorporated herein by reference.

On January 8, 2018, the Company began utilizing a new corporate presentation (the “*Corporate Presentation*”). A copy of the Corporate Presentation is attached as Exhibit 99.2 to this Current Report on Form 8-K, and is incorporated by reference herein.

In addition, the Company will be presenting at the 10<sup>th</sup> Annual Biotech Showcase Conference in San Francisco, California on Monday, January 8, 2018 at 4:00 P.M. Pacific Time.

The information in this Current Report on Form 8-K, including the information set forth in Exhibit 99.2, is being furnished and shall not be deemed “filed” for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the “*Exchange Act*”), nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as shall be expressly set forth by specific reference in such a filing.

**Item 9.01 Financial Statements and Exhibits.**

See Exhibit Index.

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**SIGNATURES**

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

**VistaGen Therapeutics, Inc.**

Date: January 8, 2018

By: /s/ Shawn K. Singh  
Shawn K. Singh  
Chief Executive Officer

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## EXHIBIT INDEX

<b>Exhibit No.</b>	<b>Description</b>
<a href="#">99.1</a>	Press Release issued by VistaGen Therapeutics, Inc., dated January 3, 2018
<a href="#">99.2</a>	Corporate Presentation, dated January 2018

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## VistaGen Therapeutics Receives FDA Fast Track Designation for AV-101 for the Treatment of Major Depressive Disorder

South San Francisco, CA (January 3, 2018) – VistaGen Therapeutics, Inc. (NASDAQ: VTGN), a clinical-stage biopharmaceutical company focused on developing new generation medicines for depression and other central nervous system (CNS) disorders, announced today that the U.S. Food and Drug Administration (FDA) has granted Fast Track Designation to AV-101 for development as a potential adjunctive treatment for Major Depressive Disorder (MDD). The FDA's Fast Track process is designed to facilitate the development and review of new treatments for serious conditions with unmet medical need such as MDD.

"Fast Track Designation is another important regulatory milestone for our AV-101 program for MDD, providing us the opportunity for frequent interactions with the FDA focused on the most appropriate and efficient development pathway to bring AV-101 to MDD patients," said Shawn Singh, Chief Executive Officer of VistaGen. "We are on track to dose the first patient in our AV-101 Phase 2 MDD adjunctive treatment study in the first quarter of 2018."

### About Fast Track Designation

Fast Track is a process designed by the FDA to facilitate the development, and expedite the review, of drugs to treat serious conditions and fill an unmet medical need. Drugs that receive Fast Track Designation may be eligible to be the subject of more frequent communications and meetings with FDA to review the drug's development plan including the design of the proposed clinical trials, use of biomarkers and the extent of data needed for approval. Drugs with Fast Track Designation may also qualify for priority review to expedite the FDA review process, if relevant criteria are met. The purpose is to get important new drugs to the patient earlier. Fast Track addresses a broad range of serious conditions. For more information about Fast Track, please visit:

<https://www.fda.gov/ForPatients/Approvals/Fast/ucm405399.htm>.

### About Major Depressive Disorder

Major Depressive Disorder (MDD) is a common but serious mood disorder in which individuals exhibit depressive symptoms, such as a depressed mood or a loss of interest or pleasure in daily activities consistently for at least a two-week period, and demonstrate impaired social, occupational, educational or other important functioning. Over 300 million people worldwide suffer from depression.<sup>1</sup> While antidepressants are widely used for treatment, large scale studies have suggested the U.S. drug-treated MDD market is substantially underserved.<sup>2,3</sup>

### About VistaGen

VistaGen Therapeutics, Inc. (NASDAQ: VTGN), is a clinical-stage biopharmaceutical company focused on developing new generation medicines for depression and other CNS disorders. VistaGen's lead CNS product candidate, AV-101, is in Phase 2 development, initially as a new generation oral antidepressant drug candidate for Major Depressive Disorder (MDD). AV-101's mechanism of action is fundamentally different from all FDA-approved antidepressants and atypical antipsychotics used adjunctively to treat MDD, with potential to drive a paradigm shift towards a new generation of safer and faster-acting antidepressants. AV-101 is currently being evaluated by the U.S. National Institute of Mental Health (NIMH) in a small Phase 2 monotherapy study in MDD being fully funded by the NIMH and conducted by Dr. Carlos Zarate Jr., Chief, Section on the Neurobiology and Treatment of Mood Disorders and Chief of Experimental Therapeutics and Pathophysiology Branch at the NIMH. VistaGen is preparing to launch a 180-patient Phase 2 study of AV-101 as an adjunctive treatment for MDD patients with an inadequate response to standard, FDA-approved antidepressants. Dr. Maurizio Fava of Harvard University is the Principal Investigator of the VistaGen's AV-101 MDD Phase 2 adjunctive treatment study. AV-101 may also have the potential to treat multiple CNS disorders and neurodegenerative diseases in addition to MDD, including neuropathic pain, epilepsy, Huntington's disease, Parkinson's disease levodopa-induced dyskinesia (PD LID) and other CNS diseases and disorders where modulation of the NMDA receptors, activation of AMPA pathways and/or key active metabolites of AV-101 may achieve therapeutic benefit.

For more information, please visit [www.vistagen.com](http://www.vistagen.com) and connect with VistaGen on [Twitter](#), [LinkedIn](#) and [Facebook](#).

**Forward-Looking Statements**

The statements in this press release that are not historical facts may constitute forward-looking statements that are based on current expectations and are subject to risks and uncertainties that could cause actual future results to differ materially from those expressed or implied by such statements. Those risks and uncertainties include, but are not limited to, risks related to the successful launch, continuation and results of the NIMH's Phase 2 (MDD monotherapy) and/or the Company's planned Phase 2 (MDD adjunctive treatment) clinical studies of AV-101, allowance of patent applications and continued protection of its intellectual property, and the availability of substantial additional capital to support its operations, including the AV-101 Phase 2 clinical development activities described above. These and other risks and uncertainties are identified and described in more detail in VistaGen's filings with the Securities and Exchange Commission (SEC). These filings are available on the SEC's website at [www.sec.gov](http://www.sec.gov). VistaGen undertakes no obligation to publicly update or revise any forward-looking statements.

<sup>1</sup> World Health Organization, 2017; Available at <http://www.who.int/mediacentre/factsheets/fs369/en/>

<sup>2</sup> Rush AJ, et al. Am J. Psychiatry. 2006, 163(11): 1905-1917 (STAR\*D Study),

<sup>3</sup> Decision Resources 2016

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DEVELOPING NEW GENERATION MEDICINES FOR DEPRESSION AND OTHER CNS DISORDERS



This presentation contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements concern our product candidates, our development efforts, our collaborations, our intellectual property, our financial condition, our plans and our development programs. These statements involve risks, uncertainties and assumptions, and are based on the current estimates and assumptions of the management of VistaGen Therapeutics, Inc. (Company) as of the date of this presentation and are subject to uncertainty and changes. Given these uncertainties, you should not place undue reliance on these forward-looking statements. Important

factors that could cause actual results to differ materially from those indicated by such forward-looking statements include, among others, those set forth in our Annual Report on Form 10-K for the year ended March 31, 2017, filed with the Securities and Exchange Commission (SEC) on June 29, 2017, as well as any updates to those risk factors filed with the SEC from time to time in our periodic and current reports on Forms 8-K and 10-Q. All statements contained in this presentation are made only as of the date of this presentation, and the Company undertakes no duty to update this information unless required by law.

www.vistagen.com

## VistaGen Overview

NASDAQ: VTGN

<p>Depression market is large, underserved and ready for new generation treatment options with fundamentally different MOAs</p>	<p>AV-101 is a new generation oral antidepressant candidate in Phase 2 development for Major Depressive Disorder (MDD)</p>	<p>Opportunities in additional CNS markets - neuropathic pain, Parkinson's disease, levodopa-induced dyskinesia and others</p>
<p>Short time line to two potentially major clinical catalysts in MDD</p>	<p>Clinical and financial support from U.S. National Institute of Mental Health (NIMH) and Dr. Carlos Zarate, Jr.</p>	<p>Experienced CNS team leading execution</p>

# Major Depressive Disorder (MDD)

SUBSTANTIAL MARKET WITH GROWING UNMET NEED

OVER  
**300 MILLION**  
PEOPLE WORLDWIDE  
SUFFER FROM  
DEPRESSION<sup>1</sup>

1 in 10 in U.S. Over Age 12  
Takes an Antidepressant<sup>2</sup>

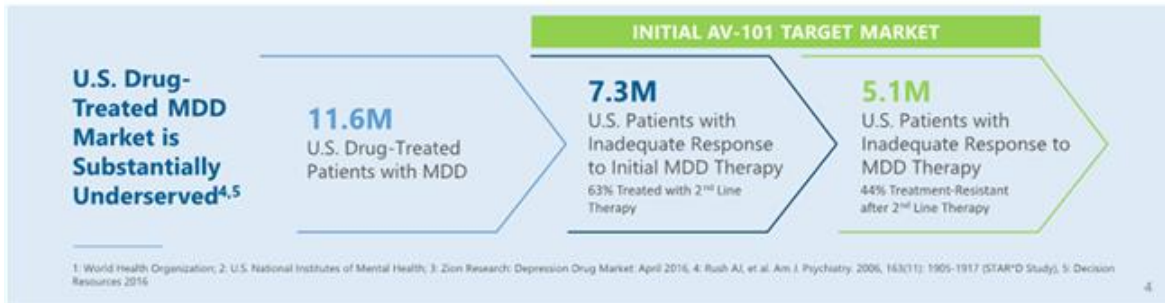


Global Depression Market  
is Expected to Grow<sup>3</sup>

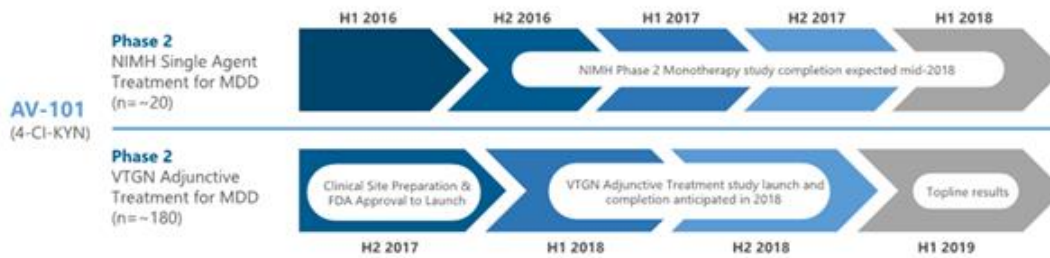
\$14.5B  
2014



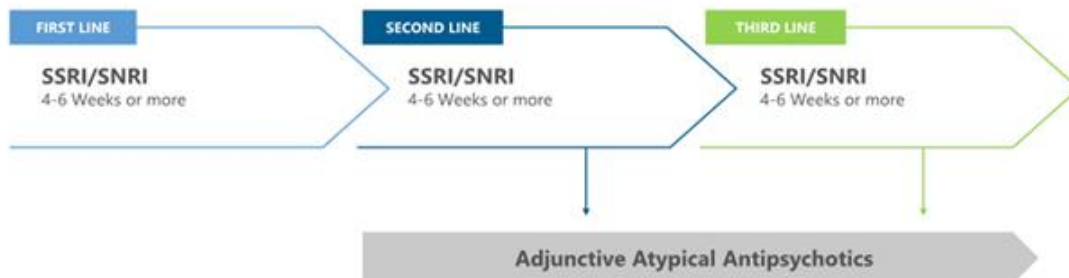
\$17 Billion+  
2020



## AV-101 MDD Pipeline



## Current MDD Drug Treatment Paradigm





## Current FDA-Approved Drug Treatments for MDD

PROBLEMS WITH CURRENT ANTIDEPRESSANTS AND ADJUNCTIVE ATYPICAL ANTIPSYCHOTICS



### Current Antidepressants

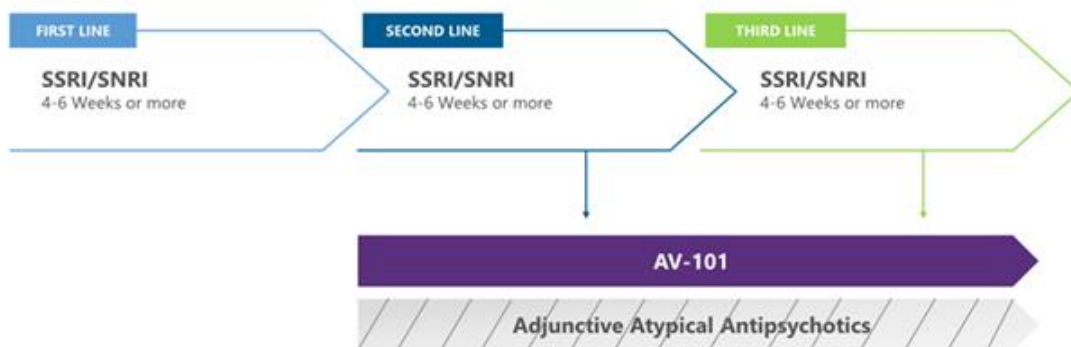
- **Often do not work**
  - Initial treatment effective in only 1 of 3 patients
- **Slow to work**
  - May take 4 to 6 weeks or more to achieve antidepressant effects
- **Side-effects**
  - Anxiety, decreased libido, nausea, sleep, disturbances, weight gain and more

### Current Adjunctive Atypical Antipsychotics

- **Limited efficacy**
  - Only 10 to 20% of MDD patients respond
- **Side effects**
  - Weight gain, metabolic syndrome, tardive dyskinesia, sedation, cognitive impairment
- **Safety concerns**
  - "Black Box" warnings - mortality in elderly, cardiovascular complications, convulsions, stroke

## VistaGen's Target Drug Treatment Paradigm for MDD

AV-101'S INITIAL FIT, AS AN ADJUNCTIVE THERAPY IN THE MDD TREATMENT ALGORITHM



AV-101 - Potential to Displace Adjunctive Atypical Antipsychotics in the MDD Drug Treatment Paradigm

## Paradigm Shift in Treatment of Major Depressive Disorder

"Recent data suggest that ketamine, given intravenously, might be the most important breakthrough in antidepressant treatment in decades."

**Thomas Insel**  
Former Director - U.S. National Institute of Mental Health<sup>1</sup>

1. <http://www.nih.nih.gov/about/directors/2014/ketamine.shtml>

# The Ketamine Story

A PARADIGM SHIFT TOWARDS NEW GENERATION ANTIDEPRESSANTS



FDA-approved anesthetic



Currently, only available by injection



Popular Club Drug: "Special K"

**NUMEROUS SAFETY CONCERNS:** confusion, dissociation, hallucinations, dizziness, increased blood pressure and heart rate, abuse potential

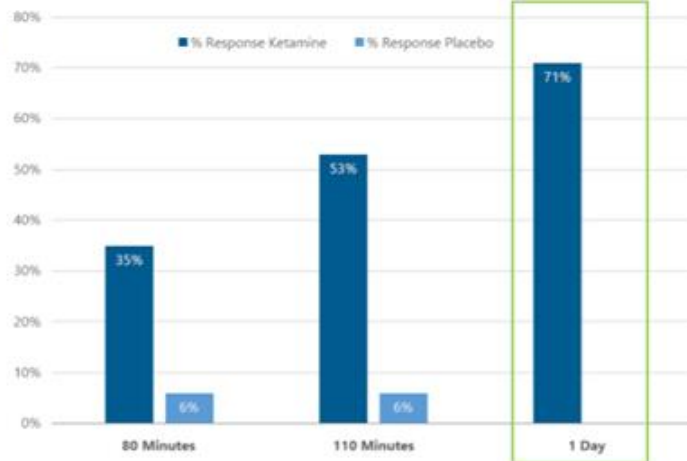
- MOA is fundamentally different from all FDA-approved antidepressants and adjunctive atypical antipsychotics
- Clinical studies at the NIMH and academic research centers in treatment-resistant MDD patients had game-changing results

# NIMH Ketamine Study

BREAKTHROUGH ANTIDEPRESSANT EFFECTS WITHIN 1 DAY OF A SINGLE TREATMENT

## Responder<sup>Y</sup> Rates at 1 Day with Ketamine in Treatment-Resistant MDD

<sup>Y</sup> Proportion of patients with treatment-resistant MDD with at least 50% improvement in depression rating



<sup>Y</sup>Zarate, C. A., Jr., et al. (2006) "A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression." *Arch Gen Psychiatry* 63:856-864.  
 Also see:  
 • Murrough, J. W., et al. (2013). "Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial." *Am J Psychiatry* 170:1134-1142.  
 • Zarate, C. A., Jr., et al. (2012) "Replication of ketamine's antidepressant efficacy in bipolar depression: a randomized controlled add-on trial." *Biol Psychiatry* 71:939-946.

# Ketamine

NEW HOPE FOR MDD PATIENTS



**Ketamine For Severe Depression:**  
'How Do You Not Offer This Drug To People?'

Drugs to Lift Depression in Hours Rather Than Weeks

THE WALL STREET JOURNAL



'Club Drug' Ketamine Provides Hope in Fight Against Depression

# AV-101 (4-Chlorokynurenine)

A POTENTIAL BREAKTHROUGH ADJUNCTIVE TREATMENT FOR MAJOR DEPRESSIVE DISORDER



## 2. ORAL, NEW GENERATION ANTIDEPRESSANT CANDIDATE

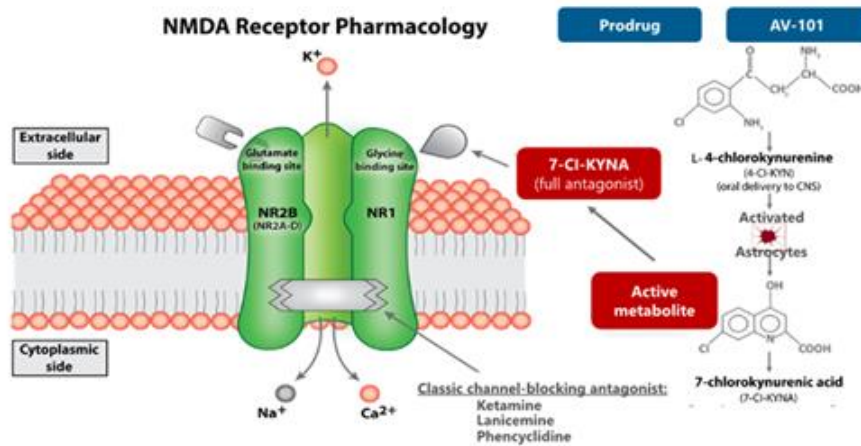
- Rapidly absorbed through the gut, actively transported into the brain, converted into its active metabolite (7-CI-KYNA), which then binds to the Gly<sub>B</sub> site of NMDA receptors

## 3. SIMILAR MOA TO KETAMINE, WITHOUT KETAMINE'S SAFETY CONCERNS

- 7-CI-KYNA inhibits NMDA receptor activity through Gly<sub>B</sub> site binding, whereas ketamine blocks the ion channel of NMDA receptors and induces psychotomimetic side effects
- Like ketamine, AV-101 demonstrates fast-acting antidepressant effects in rodent models via upregulation of AMPA receptors
- Well-tolerated in NIH-funded Phase 1 safety studies
- Drug-drug interaction and "Black Box" metabolic effects related to current antidepressants and atypical antipsychotics are not anticipated

# AV-101 (4-Chlorokynurenine) Mechanism of Action

AV-101'S METABOLITE (7-CI-KYNA) INHIBITS NMDA RECEPTOR ACTIVITY



# AV-101 vs. Ketamine

PRECLINICAL EVIDENCE OF KETAMINE-LIKE ANTIDEPRESSANT EFFECTS WITHOUT KETAMINE-LIKE SAFETY CONCERNS



The Journal of Pharmacology and Experimental Therapeutics

## "The Prodrug 4-Chlorokynurenine Causes Ketamine-Like Antidepressant Effects, but Not Side Effects, by NMDA/Glycine<sub>B</sub>-Site Inhibition"

Panos Zanos, Sean C. Piantadosi, Hui-Qiu Wu, Heather J. Pribut, Matthew J. Dell, Adem Can, H. Ralph Snodgrass, Carlos A. Zarate, Jr., Robert Schwarcz, and Todd D. Gould



## NIH Support for AV-101

VALUABLE LONG-TERM RELATIONSHIP AND SUPPORT FOR AV-101 DEVELOPMENT

### Direct funding for AV-101 Preclinical and Phase 1

\$8.8 million in direct non-dilutive cash awards for support of AV-101 preclinical development and first-in-human Phase 1 clinical safety studies

### Clinical and financial support for AV-101 Phase 2

Fully funding, and Dr. Carlos Zarate, Jr. as Principal Investigator is conducting, a small (n~20) Phase 2 MDD monotherapy clinical study in treatment-resistant MDD patients



National Institute of Mental Health



NIH and Dr. Zarate continue to drive the paradigm shift to new generation antidepressants

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## NIH-Sponsored AV-101 Phase 1 Safety Studies

NO KETAMINE-LIKE SAFETY CONCERNS

### AV-101 Phase 1a Study

- Randomized, double-blind, placebo-controlled
- Single oral dose with sequential dose-escalation
- Six single dose levels: 30, 120, 360, 720, 1,080, 1,440 mg
- 36 subjects: 18 treatment and 18 placebo; 6 per cohort

#### RESULTS

- Well-tolerated, even at maximum dose; good bioavailability; no serious adverse events
- At higher doses, some subjects on AV-101 (and none on placebo) reported positive feelings of well-being similar to antidepressant effects reported with ketamine, without ketamine's side-effects

### AV-101 Phase 1b Study

- Randomized, double-blind, placebo-controlled
- Multiple oral dose (daily for 14 days), with sequential dose-escalation
- Three dose levels: 360, 1,080 and 1,440 mg
- 48 subjects: 36 treatment and 12 placebo; 16 per cohort

#### RESULTS

- Well-tolerated, even at maximum dose; good bioavailability; no serious adverse events
- Multiple subjects on AV-101 (and none on placebo) reported positive feelings of well-being similar to antidepressant effects reported with ketamine, without ketamine's side-effects

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## NIMH-Sponsored AV-101 Phase 2 Monotherapy Study

MDD ORAL MONOTHERAPY

### Principal Investigator:

Dr. Carlos Zarate, Jr., NIMH

- Single site: NIMH
- Double-blind, placebo-controlled, crossover design
- Single oral dose monotherapy, in treatment-resistant MDD patients, once per day for 14 days
- Target enrollment: ca. 20 adult subjects

**Primary Endpoint:**  
Safety and efficacy using standard Hamilton Rating Scale (HDRS)

**Secondary Endpoints:**  
Change from baseline in other widely-accepted measures of mood, depression and cognition

MDD Monotherapy

H2 2017

H1 2018

H2 2018



NIMH completion expected

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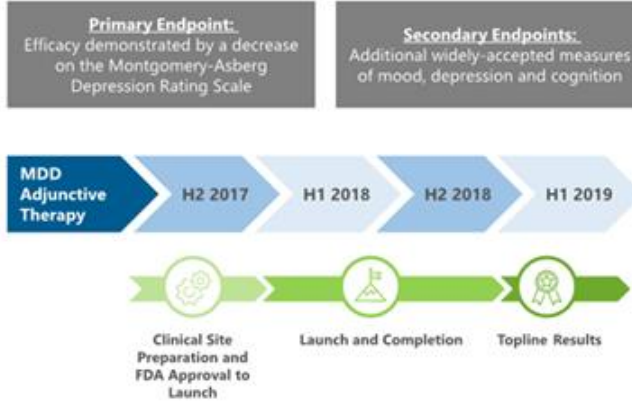
# AV-101 Phase 2 Adjunctive Treatment Study

NEW GENERATION ORAL ADJUNCTIVE TREATMENT FOR INADEQUATE SSRI/SNRI MONOTHERAPY

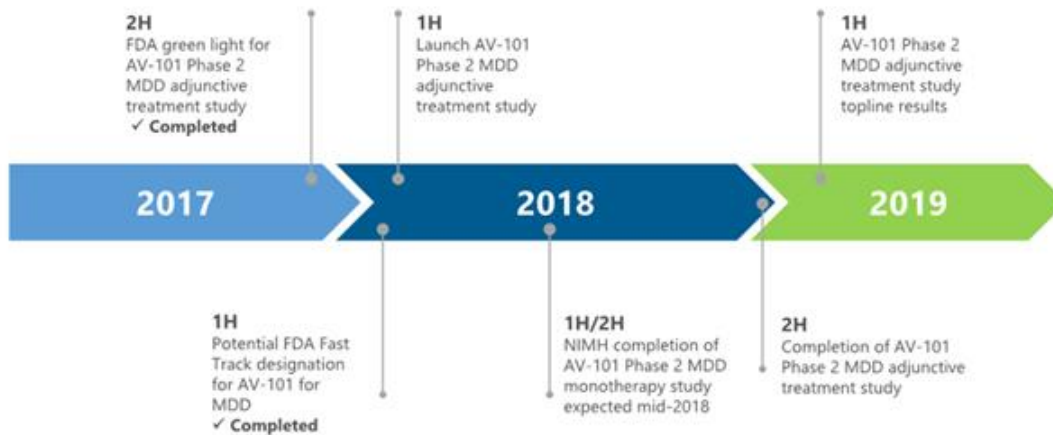
## Principal Investigator:

Dr. Maurizio Fava, Harvard University

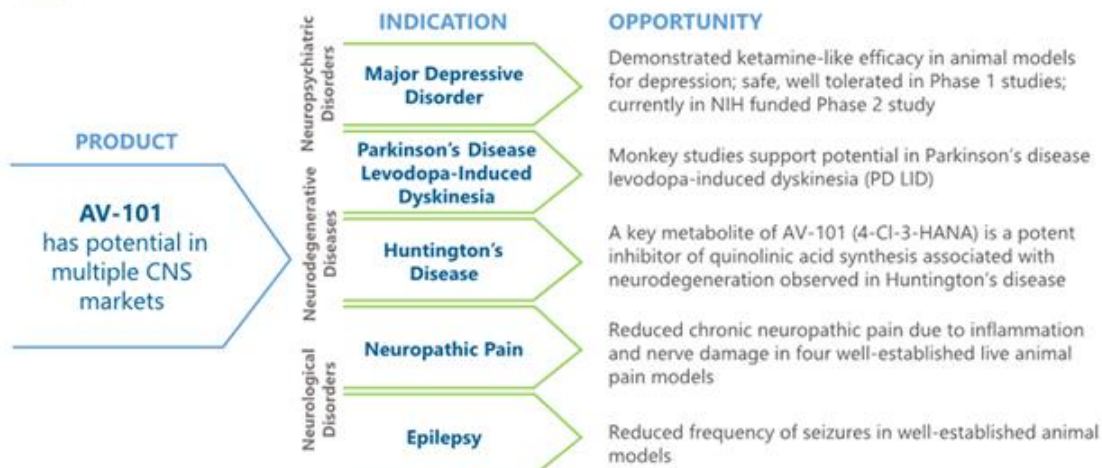
- Projected enrollment: ~180 patients
- Double-blind, placebo-controlled, 2-Stage Sequential Parallel Comparison Design (SPCD)
- **Objective:** assess efficacy and safety of AV-101 + standard antidepressants in MDD patients with an inadequate response to standard antidepressants
- Single oral dose, once per day for 14 days
- Projected launch and completion in 2018



## Short Time Horizon to Potential Clinical Catalysts



## Potential in MDD and Additional CNS Markets



## Preeminent CNS Clinical and Regulatory Advisors



### Maurizio Fava, M.D.

Professor of Psychiatry, Harvard Medical School; Director, Division of Clinical Research, Massachusetts General Hospital (MGH) Research Institute; Executive Director, MGH Clinical Trials Network and Institute

### Thomas Laughren, M.D.

Director (retired), U.S. Food and Drug Administration (FDA) Division of Psychiatry Products, Office of New Drugs, Center for Drug Evaluation and Research (CDER)

### Sanjay Mathew, M.D.

Associate Professor of Psychiatry and Behavioral Sciences, Marjorie Bintliff Johnson and Raleigh White Johnson, Jr. Chair for Research in Psychiatry and Menninger Department of Psychiatry & Behavioral Sciences, Baylor College of Medicine

### Gerard Sanacora, Ph.D., M.D.

Professor of Psychiatry, Yale School of Medicine; Director, Yale Depression Research Program; Scientific Director, Yale-New Haven Hospital Interventional Psychiatry Service

### Mark Wallace, M.D.

Professor of Clinical Anesthesiology, Chair of the Division of Pain Medicine, Medical Director and Director at the University of California, San Diego

## Experienced Team Leading Execution

### Ralph Snodgrass, Ph.D. President, Chief Scientific Officer

- 23 years of experience in senior biotechnology management
- Progenitor, Lineberger Comprehensive Cancer Center



### Shawn K. Singh Chief Executive Officer

- 25 years of experience with biopharmaceutical companies, a healthcare venture capital firm and a profitable CRO
- Artemis Neuroscience; SciClone Pharmaceuticals; Cato BioVentures; Cato Research; Morrison & Foerster



### Jerrold D. Dotson, CPA Chief Financial Officer, Secretary

- 20 years of experience in senior management finance and administration
- Calypte Biomedical; Discovery Foods; California & Hawaiian Sugar; Clorox

### Mark A. Smith, M.D., Ph.D. Chief Medical Officer

- 20 years of large Pharma CNS drug development experience
- Teva Pharmaceuticals; Shire Pharmaceuticals; AstraZeneca Pharmaceuticals; DuPont Pharmaceutical Company; U.S. National Institute of Mental Health



### Mark A. McPartland Vice President, Corporate Development

- 20 years of experience in corporate development, capital markets and management consulting
- Stellar Biotechnologies; MZ Group; Hayden Communications; Alliance Advisors

Depression market is primed for new generation drugs with MOAs that are fundamentally different from all current treatments options

AV-101 is an oral new generation antidepressant candidate with a ketamine-like MOA but without ketamine's side effects

Non-opioid neuropathic pain candidate

Opportunities in multiple large CNS markets

Potential for transformative Phase 2 clinical results in 2018 and early 2019

Valuable support from U.S. National Institute of Mental Health

Experienced CNS-focused team leading execution

**VistaGen<sup>®</sup>**  
Therapeutics

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Website: www.vistagen.com

Nasdaq: VTGN

DEVELOPING NEW GENERATION MEDICINES FOR DEPRESSION AND OTHER CNS DISORDERS

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Therapeutics

## Supplemental Information

Nasdaq: VTGN

DEVELOPING NEW GENERATION MEDICINES FOR DEPRESSION AND OTHER CNS DISORDERS

www.vistagen.com

### Board of Directors

**VistaGen<sup>®</sup>**  
Therapeutics

#### Jerry Gin, Ph.D., MBA Director

- 45 years of healthcare industry experience; Co-Founder of Oculex (acquired by Allergan for \$230M)
- Serves as Co-Founder, President and CEO of Nuvora



#### Jon S. Saxe Chairman

- 35 years of biopharmaceutical experience, director of multiple public and private healthcare companies
- Former President and Director, PDL BioPharma; CEO, Synergen (acquired by Amgen for \$262M); VP, Licensing and Corporate Development, Head of Patent Law, Hoffmann-La Roche



#### Ralph Snodgrass, Ph.D. President, CSO, Director

- 23 years of experience in senior biotechnology management
- Progenitor, Lineberger Comprehensive Cancer Center

#### Shawn Singh CEO, Director

- 25 years of experience with biopharmaceutical companies, a venture capital firm and a profitable CRO
- Artemis Neuroscience; SciClone Pharmaceuticals; Cato BioVentures; Cato Research

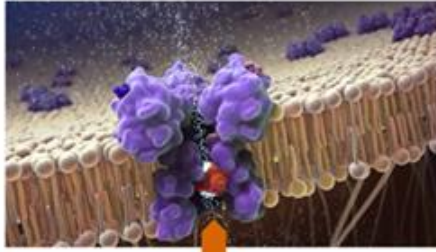


#### Brian J. Underdown, Ph.D. Director

- 30 years of leadership experience in biopharmaceutical sector; key player in growth of 10 Life Science companies;
- Former VP, Research, Pasteur Merieux Connaught (now Sanofi Pasteur); Venture Partner, Lumira Capital

## AV-101's Mechanism of Action

### Classic NMDA Receptor Channel-Blocking Antagonists Ketamine, PCP, Lanicemine



Ketamine blocks the ion channel of the NMDA receptor

### AV-101's Active Metabolite (7-Cl-KYNA) (full antagonist)

AV-101 does not block NMDA receptor activity, it inhibits it



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## AV-101 Advantages vs. NR2B Specific

### NMDA RECEPTOR ANTAGONISTS

There are 9 different variants of the NMDAR<sup>5</sup>

	Di-heteromeric NMDARs					Tri-heteromeric NMDARs			
	1/2A	1/2B	1/2C	1/2D	1/3A2	1/2A/2B	1/2A/2C	1/2B/2D	1/2B/3A
AV-101 Gly <sub>B</sub> NMDA receptor antagonist regulates	+	+	+	+	+	+	+	+	+
NR2B specific NMDA receptor antagonist regulates	-	+	-	-	-	+	-	+	+

- In addition to neuronal cell-specific expression, within individual neurons, several NMDA receptor subtypes can be expressed<sup>1</sup>
- NR2B-selective compounds can only modulate 4 of the 9 NMDA receptor variants
- AV-101 decreases NMDA receptor function on all 9 NMDA receptor variants

<sup>1</sup> Pasileti, P., et al. (2013). "NMDA receptor subunit diversity: impact on receptor properties, synaptic plasticity and disease." *Nat Rev Neurosci* 14(8): 583.

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## AV-101 vs. Ketamine in Published Preclinical Studies

Benefits	AV-101	Ketamine
Forced-swim	EQUIVALENT	EQUIVALENT
Tail-suspension	EQUIVALENT	EQUIVALENT
Learned-helplessness	EQUIVALENT	EQUIVALENT
Novelty-suppressed feeding	EQUIVALENT	EQUIVALENT
Negative Behavioral Effects	AV-101	Ketamine
Abusive potential	No	Yes
Hyper movement	No	Yes
Movement sensitization	No	Yes
Circling and rearing	No	Yes
Sensory-motor gating	No	Yes

Zanos, P., et al. (2015). "The Prodrug 4-Chlorokynuremine Causes Ketamine-Like Antidepressant Effects, but Not Side Effects, by NMDA/GlycineB-Site Inhibition." *J Pharmacol Exp Ther* 355(1): 76-85.

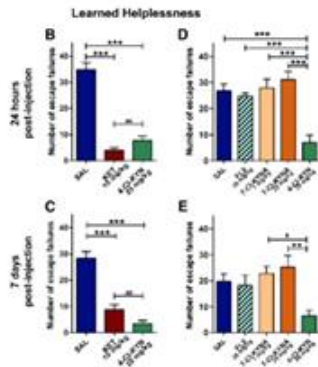
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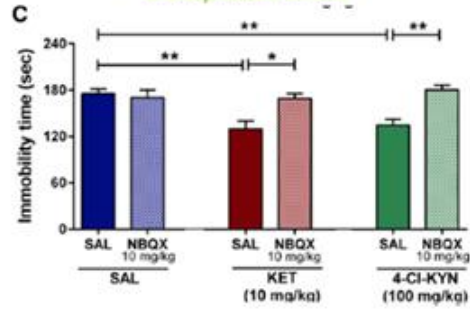
## AV-101 and Ketamine

SIMILAR EFFICACY IN PUBLISHED PRECLINICAL STUDIES

A single dose of AV-101 demonstrated acute (24 h) and chronic (7 d) antidepressant effects similar to ketamine

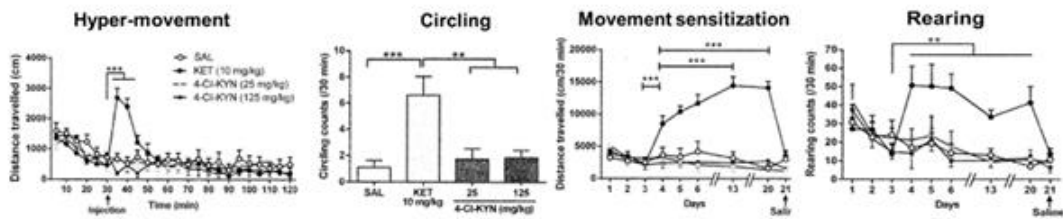


NBQX (AMPA antagonist) blocks AV-101 effects which supports AMPA receptor activation as necessary for rapid-onset, NMDAR-mediated antidepressant effects



Zanos, P., et al. (2015). "The Prodrug 4-Chlorokynurenine Causes Ketamine-Like Antidepressant Effects, but Not Side Effects, by NMDA/GlycineB-Site Inhibition." *J Pharmacol Exp Ther* 355(1): 76-85.

## AV-101 Had No Negative Behavioral Effects of Ketamine in Published Preclinical Studies



Zanos, P., et al. (2015). "The Prodrug 4-Chlorokynurenine Causes Ketamine-Like Antidepressant Effects, but Not Side Effects, by NMDA/GlycineB-Site Inhibition." *J Pharmacol Exp Ther* 355(1): 76-85.

## AV-101 for Parkinson's disease levodopa-induced dyskinesia (PD LID)

### UNMET MEDICAL NEED

Levodopa is the most effective treatment for Parkinson's disease (PD), but levodopa therapy is typically reserved for later in the course of the disease because it causes PD LID in a significant number of cases

### RATIONALE

Weak NMDA antagonists, such as amantadine, are approved for PD LID, but have significant side effects

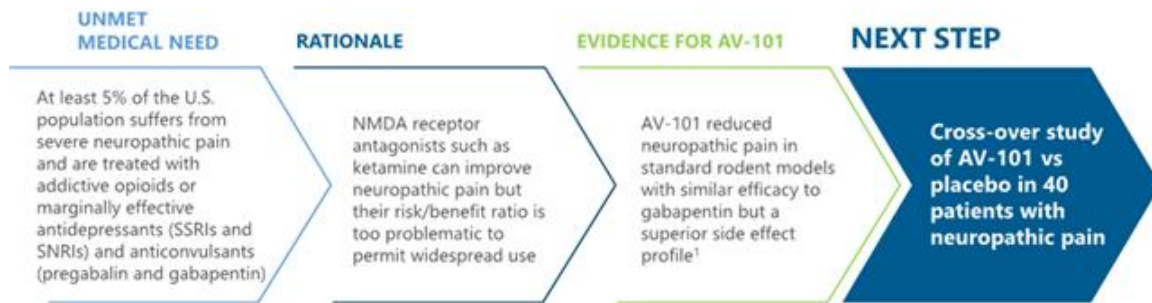
### EVIDENCE FOR AV-101

AV-101 reduced mean dyskinesia scores by 30% in Parkinsonian monkeys with LID without affecting Parkinson's symptoms

### NEXT STEP

Cross-over study of AV-101 vs placebo in 30 Parkinson's patients

## AV-101 for Neuropathic Pain



<sup>1</sup> Yaksh, T.L., et al. (2017). "Characterization of the Effects of L-4-Chlorokynuremine on Nociception in Rodents." *The Journal of Pain* 18: 1164-1196.

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## VistaStem

CARDIAC STEM CELL TECHNOLOGY FOR REGENERATIVE MEDICINE AND DRUG RESCUE

**THE WALL STREET JOURNAL.** "Bayer Teams Up With Versant Ventures to Develop Stem-Cell Therapies"  
December 2017

- Key participant in FDA's Comprehensive *in vitro* Proarrhythmia Assay (CiPA) initiative focused on next generation, stem cell-based predictive cardiotoxicity for drug development and drug rescue
- Exclusive sublicense of cardiac stem cell technology to BlueRock Therapeutics for development and commercialization of regenerative medicine and cellular therapies to treat heart disease



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## Regenerative Medicine Opportunities



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## Publications

- Abbasi J. Ketamine Minus the Trip: New Hope for Treatment-Resistant Depression. *JAMA*. Published online November 08, 2017. doi:10.1001/jama.2017.12975
- Yaksh, T.L., et al. (2017). "Characterization of the Effects of L-4-Chlorokynurenine on Nociception in Rodents." *The Journal of Pain* 18: 1184-1196.
- Li, C., et al. (2016) "Activation of hippocampal BDNF signaling is involved in the antidepressant-like effect of the NMDA receptor antagonist 7-chlorokynurenic acid." *Brain Research* 1630:73-82
- Gerhard, D. M., et al. (2016) "Emerging treatment mechanisms for depression: focus on glutamate and synaptic plasticity." *Drug Discov Today* 21:454-464
- Bay-Richter, C., et al. (2015) "A role for inflammatory metabolites as modulators of the glutamate N-methyl-D-aspartate receptor in depression and suicidality." *Brain Behav Immun* 43:110-117
- Zanos, P., et al. (2015) "The Prodrug 4-Chlorokynurenine Causes Ketamine-Like Antidepressant Effects, but Not Side Effects, by NMDA/GlycineB-Site Inhibition." *J Pharmacol Exp Ther* 355:76-85
- Preskorn, S., et al. (2015) "Randomized proof of concept trial of GLYX-13, an N-methyl-D-aspartate receptor glycine site partial agonist, in major depressive disorder nonresponsive to a previous antidepressant agent." *J Psychiatr Pract* 21:140-149.
- Murrough, J. W., et al. (2013) "Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial." *Am J Psychiatry* 170:1134-1142
- Schwarcz, R., et al. (2012) "Kynurenes in the mammalian brain: when physiology meets pathology." *Nat Rev Neurosci* 13:465-477
- Zarate, C. A., Jr., et al. (2006) "A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression." *Arch Gen Psychiatry* 63:856-864
- Moskal, J. R., et al. (2005) "GLYX-13: a monoclonal antibody-derived peptide that acts as an N-methyl-D-aspartate receptor modulator." *Neuropharmacology* 49:1077-1087.